REMARKS

Claims 1-4 and 7-8 are pending in the instant application. Claims 1 and 8 are independent. Applicants have canceled claims 5 and 9-12 without prejudice to the subject matter therein. Applicants amended claim 2 to correct an antecedent basis. Table B, on page 14a provides support for the structures in amended claim 2. Applicants have not raised any issues of new matter.

Issue Under 35 U.S.C. §112

Claims 2 and 10 stands rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. The Examiner asserts that claims 2 and 10 are not within the metes and bounds of claims 1 and 9, respectively.

Applicants have canceled claim 10 and amended claim 2 such that it is within the scope of the metes and bounds of claim 1.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

Issue Under 35 U.S.C. §103(a)

Claims 1-5 and 7-12 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Lobaccaro et al. (J. Med.

Chem., 1997, 40, 2217-2227). Applicants assert that patentable distinctions exist between the present invention and Lobaccaro et al.

Distinctions Between the Present Invention and Lobaccaro et al.

Lobaccaro et al. discloses that the 11β position of the steroid in intermediate compounds 5a-b is substituted with ethyl, butyl chains. *See Scheme 1, page 2218*. Scheme 3, page 2219 of Lobaccaro et al. discloses that the 11β position of the steroid has a C10 chain with either TBDMS blocking a terminal hydroxyl group, a hydroxyl or a tosylate.

Lobaccaro et al. fails to disclose a steroid compound of formula I, wherein R^{11} is a hydrocarbon group which may be linear, or branched comprising one singular linear chain having a length of from 5 to 9 carbon atoms as the longest chain. The Examiner asserts that compounds 5a-b in scheme 1 of Lobaccaro et al. render the present invention obvious because the alkyl chains at the 11 position are homologs.

Applicants disagree with the Examiner's assertions. Compounds 5a and 5b in Scheme 1 of Lobaccaro et al have butenyl and vinyl at the 11 position. More importantly, Lobaccaro et al only discloses these compounds as intermediates in a synthetic pathway. In Tables 1 and 2 of Lobaccaro et al, compound 5b is an agonist and to achieve an antagonist Lobaccaro et al have

made derivatives with mesylate, tosylate, etc. Lobaccaro et al. only discloses a decyl 11β-alkyl chain with a tosylate; therefore, Lobaccaro fails to have any data to predict longer alkyl chains than 4 carbons. "[I]t appears that the threshold which separates estrogenic from antiestrogenic compounds is rapidly reached when the size of the 11β-alkyl chain increases, with a threshold between C-2 and C-4." *See page 2223, left column, second paragraph.*

Applicants have asserted that Lobaccaro et al. fails to disclose a steroid with an 11β-alkyl chain having ten carbons. Lobaccaro et al. only discloses tosylate, hydroxyl or TBDMS substituted decyl chain. *See Scheme 3.* Therefore, Lobaccaro et al. fails to disclose a homolog of an alkyl C9 chain.

As previously presented in a response, Lobaccaro et al. only discloses an 11β-alkyl chain without any longer alkyl chains than four carbons; thus, a skilled artisan would not be motivated to make the claimed compounds having 5-9 carbons in chain length. Applicants will discuss the unexpected results in greater detail below in describing the attached 37 C.F.R. §1.132 Declaration.

Therefore, Applicants respectfully submit that a *prima facie* case of obviousness has not been presented and therefore, request withdrawal of the 35 U.S.C. §103(a) rejection.

Issue Under 35 U.S.C. §103(a)

Claims 1-5 and 7-12 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Napolitano et al. (J. Med. Chem., 1995, 38, 2774-2779). Applicants assert that patentable distinctions exist between the present invention and Napolitano et al.

Distinctions Between the Present Invention and Napolitano et al.

Napolitano et al. discloses that the 11β position of the steroid is substituted or unsubstituted short chain alkyl groups (less than five carbon atoms). In Table 1, page 2776, Napolitano et al exclusively recites alkyl chains of 2 to 4 carbons in length. However, the Examiner asserts that a skilled artisan would be motivated to extend the carbon chain and expect similar results.

Applicants claim a specific range for the chain length at the 11β position. Applicants assert that unexpected results show that this specific range identifies a series of compounds that have a specific agonist and antagonist profile, which a skilled artisan would not have known. Therefore, any argument of obviousness is overcome because a skilled artisan would not have

had a reasonable expectation of success of achieving the selectivity of the present invention. See below for a more detailed explanation of the unexpected results.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Unexpected Results

Applicants assert that a *prima facie* case of obviousness has not been established. However, if the Examiner maintains that a proper *prima facie* case of obviousness exists; Applicants present the following data and arguments that unexpected results are present. Applicants have recited that compounds 3, 5, 6, 8 and 11, which are the present invention, are agonist at ER-α and antagonist at ER-β. Compounds 1, 2, 4, 7 and 9-10 are agonist at both ER-α and ER-β. Compounds 4 and 5 only differ by one carbon in the side chain at position 11, yet 4 is an agonist ER-β and 5 is an antagonist at ER-β. The same can be said for the difference in compounds 10 and 11.

Applicants now present a 37 C.F.R. §1.132 Declaration where Mr. Antwan Ederveen declares that the series of pharmaceutical compositions claimed within the present application are agonist at ER-α and antagonist at ER-β. In a comparison with compounds

from the cited prior art, the Declarant concludes that substantially similar compounds produced different functional effects at both estrogen receptors subtypes α and β. Compounds 2 and 3 only differ by one carbon in the side chain at position 11, yet 2 is an agonist ER-β and 3 is an antagonist at ER-β. The Declarant resubmits that the homologues demonstrate different results that are unexpected and do not follow the teachings of either Lobaccaro et al. or Napolitano et al.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection because the declared unexpected results clearly overcome any *prima facie* case of obviousness.

Conclusion

Applicants submit that every issue raised by the Office Action mailed January 30, 2004 has been addressed and rebutted. Therefore, the present claims define patentable subject matter and are in condition for allowance.

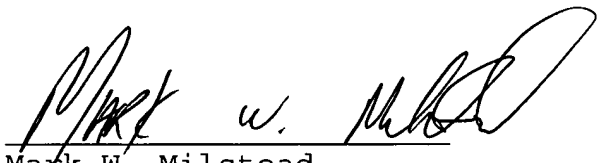
Should the Examiner believe that an Interview would be helpful in advancing the prosecution of this application, he is invited to telephone Applicants' Attorney at the number below.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicants respectfully petition for a three month extension of time for filing a response in connection with the present application.

Please charge the required fee of $940 to Deposit Account No. 02-2334.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,



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Enclosure: 37 C.F.R. §1.132 Declaration

MWM